Remarks

Claims 1-71 are pending in the subject application. Of these claims, claims 13-51 are withdrawn from consideration as being directed to non-elected subject matter and claims 1-11, 52-65, and 67-71 have been rejected. Claims 12 and 66 have been objected to as being dependent upon a rejected base claim, but allowable if rewritten in independent form, including all the limitations of the base claim and any intervening claims. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Claims 1-6, 10, 11, 54-62, 64, 65, and 69 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Kopp *et al.* This rejection is respectfully traversed.

As the Patent Office is aware, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 1 is directed to:

> A device comprising:
>
> a microfluidic substrate comprising at least one pathway for sample flow; and said microfluidic substrate further comprising at least one temperature regulated zone which is capable of cycling between at least two temperatures, said at least one temperature regulated zone being adapted to bring at least a portion of said sample pathway to said at least two temperatures while a sample is continuously flowing along said at least a portion of said sample pathway.

Applicants respectfully submit that Kopp *et al.* do not disclose the feature of a "temperature regulated zone which is capable of cycling between at least two temperatures", as required by claim 1. Applicants further submit that Kopp *et al.* fail to teach temperature regulated zones adapted to bring at least a portion of said sample pathway to at least two temperatures while a sample is continuously flowing along at least a portion of said sample pathway. Rather Kopp *et al.* show multiple fixed temperature zones (see Figure 1 of Kopp *et al.*), through which the pathway must pass; additionally, each fixed temperature zone is only capable of bringing a sample to only one temperature as the sample moves through the pathway. Additionally, the Office Action admits that

Kopp *et al.* fails to teach a device that is capable of cycling between at least two temperatures (see Office Action, paragraph 13). Accordingly, it is respectfully submitted that the claims (*i.e.*, claim 1 and those claims dependent therefrom) are not anticipated by the reference and reconsideration and withdrawal of the rejection is respectfully requested.

Claims 7-9, 63, 67, 68, 70, and 71 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Kopp *et al.* in view of Wilding *et al.* (U.S. Patent No. 5, 498,392). The Office Action asserts that one skilled in the art would have been motivated to combine the teachings of Wilding *et al.* with those of Kopp *et al.* in order to allow for the processing of samples simultaneously; however, the Office Action fails to indicate why one of ordinary skill in the art would have been motivated to substitute the sample chamber of Wilding *et al.* into the device of Kopp *et al.* This rejection is respectfully traversed for the following reasons.

In determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. *In re Taborsky*, 502 F.2d 775, 780, 183 U.S.P.Q. 50, 55 (C.C.P.A. 1974). For example, the Office Action must indicate the reasons why one skilled in the art would have substituted the sample chamber of Wilding *et al.* into the device of Kopp *et al.* Absent such reasons or incentives, the teachings of the references are not combinable. Furthermore, it is well-settled law that if, when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. *In re Sponnoble*, 405 F.2d 578, 587, 160 U.S.P.Q. 237, 244 (C.C.P.A. 1969); see also *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose).

As indicated *infra*, Wilding *et al.* do not disclose a device for continuous flow, but rather a device permitting the miniaturization of a batch process. In that it relates to a device for a batch process, one of skill in the art would not be lead to combine it with Kopp *et al.* who teach a continuous flow device. Further, while Wilding *et al.* teach a heating and cooling means so that the device can heat and cool a reaction chamber 22A, the temperature changes in Wilding *et al.* do not take place while the sample is flowing, but rather while it is stationary in reaction chamber 22A (see Figure 11, and description bridging columns 14 and 15).

Thus, it is respectfully submitted that one of ordinary skill in the art would not have been motivated to modify the teachings of Kopp *et al.* with the teachings of Wilding *et al.* to replace multiple fixed-temperature zones with a temperature regulated zone that cycles between at least two temperatures. Indeed, Wilding *et al.* teaches two kinds of processes: in one, depicted in Figure 10, the sample is moved from one constant temperature vessel to another (an embodiment that does not meet the limitations of the claimed invention); and a second, depicted in Figure 11, where the sample is subjected to variable temperature in a single vessel. Both of these processes are "batch processes", and not continuous flow processes (*e.g.*, the sample chamber is sealed during temperature cycling (see paragraph bridging columns 14-15)). It is respectfully submitted that the modification of the continuous flow device of Kopp *et al.* with the teachings of Wilding *et al.* (particularly as relates to the use of a single PCR chamber, *i.e.*, the process of Figure 11) would have rendered the device of Kopp *et al.* incapable of functioning as a continuous flow device and one of ordinary skill in the art would not have been motivated to combine the references. Applicants also note that Kopp *et al.* teach away from the use of a cycling temperature zone. For example, the authors state, at page 1046, column 3, last paragraph:

> A continuous-flow PCR system can be realized by a time-space conversion in the PCR system-that is, by keeping temperatures constant over time at different locations in the system and moving the sample through the individual temperature zones.

Accordingly, it is respectfully submitted that the combination of Kopp *et al.* and Wilding *et al.* fails to establish a *prima facie* case of obviousness and withdrawal of the rejection is respectfully requested.

Conventional PCR is a batch process, with the reaction being carried out in a single vessel that is alternately heated to different temperatures. Wilding *et al.* describe a miniaturized version of conventional PCR, in which the reactions take place in reaction chambers 22 that are alternately heated to different temperatures. In a batch process, each device carries out a single reaction at a time.

The subject invention also possesses a variety of advantages over the cited prior art. For example, the use of a temperature-regulated zone which a capable of cycling between at least two temperatures has important advantages over Kopp *et al.*: Kopp *et al.* teach a serpentine pathway (see Figure 1) in which a single pathway passes multiple times sequentially through different fixed temperature zones. This arrangement requires a large amount of surface area per single pathway, meaning that the ratio of surface area required to volume of sample (A/V) is very high. In the device of the invention, in one embodiment, the pathway need pass through only a single temperature cycled region, meaning very little surface area is required per pathway. This greatly diminishes the surface area of device required to treat a given volume.

Furthermore, each heat zone of the Kopp reference must be separated by a sufficient distance from another heat zone to guarantee a standardized temperature in the isothermal zones. In contrast, the device of the invention can subject the sample to different temperatures in a single temperature-regulated zone, and hence no requirement for spatial separation. The device of invention therefore facilitates miniaturization. In the device of Kopp *et al.*, it is also necessary to have as many fixed temperature heat zones as there are different temperatures in a reaction cycle. In contrast, in the device of the invention, an essentially infinite number of temperature zones are possible, simply by varying the temperature program of the temperature-regulated zone(s).

The teachings of Kopp *et al.* further require that the flow pathway must pass through multiple fixed-temperature zones. This requires that the channels be longer than those of this invention, in which the pathways may pass through only a single *cycling* temperature-regulated zone. Longer channels require a higher pressure, causing problems with the implementation with the Kopp *et al.* device and rendering the device more complicated and expensive. Indeed, it appears that the only way the user can change the number of cycles in the Kopp *et al.* device is by changing the number of passages through the fixed-temperature zones. This requires the construction of an entirely new device. In contrast with the device of the invention, the number of cycles can be changed simply by reprogramming the number of temperature cycles of the temperature-regulated zone, and/or by changing the flow rate. In PCR, the number cycles is *routinely* changed from one sample to another, for example, if the DNA to be amplified is present at very low concentrations. The device of the invention can be readily adapted to each and every PCR reaction, whereas the device of Kopp *et al.*

cannot be so adapted without physically changing the device itself (*e.g.*, by adding additional channels or additional temperature controlled zones).

As the Patent Office is aware, in reactions, such as PCR, the duration of each reaction step (*i.e.*, 1. template denaturation of double-stranded DNA, 2. primer annealing, and 3. primer extension) must be independently adjusted from sample to sample. Template denaturation depends on the length of the DNA to be amplified (longer DNAs take longer to denature). Primer annealing depends on the length of the primer (shorter primers will anneal faster than longer ones). Primer extension depends on the length of the DNA being amplified (longer DNA require longer extension times). The DNA to be amplified changes from sample to sample, as do the primers used. This means that for each sample it may be desirable to optimize the time the sample passes through each temperature ($t_{denaturation}$, $t_{annealing}$ and $t_{extension}$) *independently*. This is not possible with the device of Kopp *et al.* The only parameter that Kopp *et al.* can change without constructing an entirely new device is the sample flow rate. Changing the sample flow rate in the Kopp *et al.* device will change the time spent at each temperature, but not in an *independent* way. For example, if the flow rate is decreased by a factor of 2, the time spent at every temperature will double. In contrast, in the device of the invention, the duration of each cycle temperature can be changed simply by reprogramming the device that controls the cycling temperature zone. It is therefore possible to independently vary the denaturation time, the annealing time and the extension time.

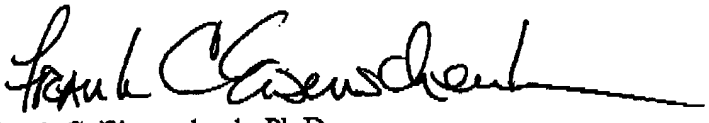
Additionally, conventional PCR is a batch process, with the reaction being carried out in a single vessel that is alternately heated to different temperatures. Wilding *et al.* describe a miniaturized version of conventional PCR, in which the reactions take place in reaction chambers 22 that are alternately heated to different temperatures. In a batch process, each device carries out a single reaction at a time. With continuous flow, in contrast, multiple reactions are carried out in a series in the same device. (For example, in Example 1 of the present application, it is possible to treat five PCR samples per channel every 30 minutes, whereas in the device of Wilding *et al.*, only 1 sample can be treated in 30 minutes). Furthermore, the device disclosed by Wilding *et al.* is intended for single-use, after which the device is discarded (see column 3, line 2 and column 5, line 61). In contrast, continuous flow systems carry out multiple reactions in series, essentially indefinitely (*i.e.*, the system is essentially indefinitely reusable, rather than disposable). Thus, it is respectfully

submitted that one skilled in the art would not have been motivated to combine the teachings of Wilding *et al.* with those of Kopp *et al.*. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

In view of the foregoing remarks and the amendments to the claims, Applicants believe that the pending claims are now in condition for allowance, and such action is respectfully requested. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Petition for Two-Month Extension of Time
Revocation of Power of Attorney